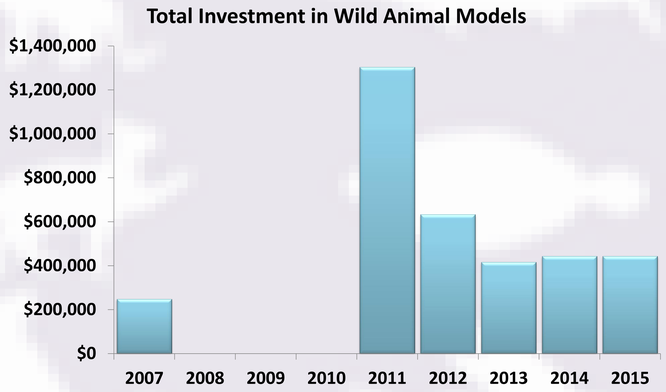
# NIH Portfolio Analysis for the use of Wild Animal Models in Order to Advance the Understanding of Human Behavior and Disease

**Background:**
The use of animal models—species for which a broad range of diagnostic, molecular, and genetic tools have been developed—in tightly controlled laboratory environments has been instrumental in driving progress in the biomedical sciences. However, in natural populations, disease processes operate in the context of enormous genetic, phenotypic, and environmental variability. Understanding diseases in animal populations (including humans) thus requires investment in "wild animal models" that explicitly include individual variation and relevant environmental gradients. Wild mammal groups such as primates, rodents, and ungulates have been identified as potentially useful models of diseases in the wild and can provide context, tools, and opportunity for cutting-edge research at the interface of ecological and biomedical sciences.

**Purpose of portfolio analysis:**
To determine total FY07-FY15 NIH investment in research aimed at the development and/or utilization of wild animal models to investigate human disease, behavior and social conditions.

**Methods:**
QVR search using the key words "wild animal model" OR "natural animal model" in the abstract, title and the summary statement. Search included awarded and non-awarded applications between the years of FY2007-FY2015. For comparison to NIH investment in all animal models, the keyword (RCDC) "animal model" was used and the search included all awarded grants from FY2007-FY2015.




**Number of Awarded Grants**

| | Total Number of Grants Awarded Utilizing Animal Models | Total Number of Grants Awarded Utilizing Wild Models |
|---|---|---|
| **2007** | 5654 | 1 |
| **2008** | 6163 | 0 |
| **2009** | 7952 | 0 |
| **2010** | 7504 | 0 |
| **2011** | 6730 | 3 |
| **2012** | 7081 | 2 |
| **2013** | 6970 | 1 |
| **2014** | 7052 | 1 |
| **2015** | 4954 | 1 |
| | **60060** | **9** |

**Portfolio Analysis for Wild Animal Models FY07-FY15**

| | | Total Applications | Grants funded | Total Funding |
|---|---|---|---|---|
| Areas of Interest: | 1. Modeling cancer/cancer spread | 1 | 1 | $247,281 |
| | 2. Modeling behavior and social interactions | 3 | 0 | $0 |
| | 3. Modeling communicable/infectious diseases | 17 | 7 | $2,628,262 |
| | 4. Immunological studies | 7 | 0 | $0 |
| | 5. Genetic studies of disease | 4 | 1 | $611,633 |
| | 6. Behavior, behavioral genetics | 7 | 0 | $0 |
| | 7. Physiological studies | 4 | 0 | $0 |
| Total Invested: | | 43 | 9 | $3,487,176 |
| | | | | |
| Funding by Mechanism: | R01 | 17 | 6 | $2,457,543 |
| | R03 | 2 | 0 | $0 |
| | R15 | 3 | 0 | $0 |
| | R21 | 13 | 3 | $418,000 |
| | R24 | 2 | 1 | $611,633 |
| | R41 | 1 | 0 | $0 |
| | P01 | 3 | 0 | $0 |
| | F32 | 1 | 0 | $0 |
| | K01 | 1 | 0 | $0 |

| | Animal | Number of Applications | Theme | Number of Applications by Theme | Grants Funded | Total Amount |
|---|---|---|---|---|---|---|
| Animal models used: | Feline | 12 | Infectious (FIV, Herpes) | 10 | 5 | $2,210,262 |
| | | | Genetic/ physiological | 2 | 0 | $0 |
| | Canine | 2 | Behavioral (OCD) | 1 | 0 | $0 |
| | | | Immune (autoimmune) | 1 | 0 | $0 |
| | Avian | 4 | Behavioral genetics | 3 | 0 | $0 |
| | | | Cancer formation (herpes) | 1 | 1 | $247,281 |
| | Equine | 6 | Immune (autoimmune) | 6 | 0 | $0 |
| | Fish/Squid | 8 | Genetics | 3 | 1 | $611,633 |
| | | | Infectious | 5 | 2 | $418,000 |
| | | | Physiology | 1 | 0 | $0 |
| | | | Behavior (anorexia) | 1 | 0 | $0 |
| | Nonhuman primate | 5 | Behavior/ Social | 3 | 0 | $0 |
| | | | Social/ Demographic Social/ Infectious | 2 | 0 | $0 |
| | Other (Cervid, Bovine, Ursine, AGS) | 4 | Physiology | 2 | 0 | $0 |
| | | | Infectious | 2 | 0 | $0 |

## Recent publications that utilize wild animal models.

### *Carcinogenesis*

**Common cancer in a wild animal: the California sea lion (Zalophus californianus) as an emerging model for carcinogenesis**
**Browning HM, Gulland FMD, Hammond JA, Colegrove KM, Hall AJ, Phil. Trans. R. Soc. B. (2015) 370: 20140228**
"Naturally occurring cancers in non-laboratory species have great potential in helping to decipher the often complex causes of neoplasia. Wild animal models could add substantially to our understanding of carcinogenesis, particularly of genetic and environmental interactions, but they are currently underutilized. Studying neoplasia in wild animals is difficult and especially challenging in marine mammals owing to their inaccessibility, lack of exposure history, and ethical, logistical and legal limits on experimentation. Despite this, California sea lions (Zalophus californianus) offer an opportunity to investigate risk factors for neoplasia development that have implications for terrestrial mammals and humans who share much of their environment and diet. A relatively accessible California sea lion population on the west coast of the USA has a high prevalence of urogenital carcinoma and is regularly sampled during veterinary care in wildlife rehabilitation centres. Collaborative studies have revealed that genotype, persistent organic pollutants and a herpesvirus are all associated with this cancer. This paper reviews research to date on the epidemiology and pathogenesis of urogenital carcinoma in this species, and presents the California sea lion as an important and currently underexploited wild animal model of carcinogenesis."

### *Obesity*

**Canaries in the coal mine: a cross-species analysis of the plurality of obesity epidemics**
**Klimentidis YC, Beasley TM, Lin H-Y, Murati G, Glass GE, Guyton M, Newton W, Jorgensen M, Heymsfield SB, Kemnitz J, Fairbanks L, Allison DB, Proc. R. Soc. B (2011) 278, 1626–16329**
**"**A dramatic rise in obesity has occurred among humans within the last several decades. Little is known about whether similar increases in obesity have occurred in animals inhabiting human-influenced environments. We examined samples collectively consisting of over 20 000 animals from 24 populations (12 divided separately into males and females) of animals representing eight species living with or around humans in industrialized societies. In all populations, the estimated coefficient for the trend of body weight over time was positive (i.e. increasing). The probability of all trends being in the same direction by chance is 1.2. Surprisingly, we find that over the past several decades, average mid-life body weights have risen among primates and rodents living in research colonies, as well as among feral rodents and domestic dogs and cats. The consistency of these findings among animals living in varying environments, suggests the intriguing possibility that the aetiology of increasing body weight may involve several as-of-yet unidentified and/or poorly understood factors (e.g. viral pathogens, epigenetic factors). This finding may eventually enhance the discovery and fuller elucidation of other factors that have contributed to the recent rise in obesity rates."

### *Infectious Disease*

**Herpesviruses--a zoonotic threat?**
**Tischer BK, Osterrieder N, Vet Microbiol (2010) 140, 266-70**
"Herpesviruses are highly host specific and share a long synchronous evolution with their hosts. Only in rare cases, species barriers fall and allow animal to human or human to animal transmission. Among the zoonotic herpesviruses, Cercopithecine herpesvirus 1 is the most significant and can be transmitted from macaques to human. Conversely, Human herpesvirus 1 is capable of causing severe disease in primates. Besides those two examples, there are several herpesviruses with a certainly limited or only suspected ability to cross species barriers. Those include Saimiriine herpesvirus 2, Phocid herpesvirus 2, Equid herpesvirus 1, Epstein-Barr Virus, Marek's disease virus, and Pseudorabies virus. Concerning xenotransplantations, porcine gammaherpesviruses must be considered as a zoonotic threat."

**OPINION Wild immunology**
**Pedersen AB & Babayan SA, Molecular Ecology (2011) 20, 872–880.**
"In wild populations, individuals are regularly exposed to a wide range of pathogens. In this context, organisms must elicit and regulate effective immune responses to protect their health while avoiding immunopathology. However, most of our knowledge about the function and dynamics of immune responses comes from laboratory studies performed on inbred mice in highly controlled environments with limited exposure to infection. Natural populations, on the other hand, exhibit wide genetic and environmental diversity. We argue that now is the time for immunology to be taken into the wild. The goal of 'wild immunology' is to link immune phenotype with host fitness in natural environments. …. From this approach, ecologists will gain new insight into mechanisms relevant to host health and fitness, while immunologists will be given a measure of the real-world health impacts of the immune factors they study. Thus, wild immunology can be the missing link between laboratory-based immunology and human, wildlife and domesticated animal health."

**Wild Primate Populations in Emerging Infectious Disease Research: The Missing Link?**
**Wolfe ND, Escalante AA, Karesh WB, Kilbourn A, Spielman A, Lal AA,** *Emerging Infectious Diseases, Vol. 4, No. 2, April–June 1998*
"Wild primate populations, an unexplored source of information regarding emerging infectious disease, may hold valuable clues to the origins and evolution of some important pathogens. Primates can act as reservoirs for human pathogens. As members of biologically diverse habitats, they serve as sentinels for surveillance of emerging pathogens and provide models for basic research on natural transmission dynamics. Since emerging infectious diseases also pose serious threats to endangered and threatened primate species, studies of these diseases in primate populations can benefit conservation efforts and may provide the missing link between laboratory studies and the well-recognized needs of early disease detection, identification, and surveillance."

**Model or meal? Farm animal populations as models for infectious diseases of humans**
**Lanzas C, Ayscue P, Ivanek R , Gröhn YT, Nature Reviews, Microbiology (2010) 8, 139-148.**
"In recent decades, theory addressing the processes that underlie the dynamics of infectious diseases has progressed considerably. Unfortunately, the availability of empirical data to evaluate these theories has not grown at the same pace. Although laboratory animals have been widely used as models at the organism level, they have been less appropriate for addressing issues at the population level. However, farm animal populations can provide empirical models to study infectious diseases at the population level".

### *Environmental Hazards*

**The use of wild animal models to detect evidence of environmental contamination by asbestos-like substance**
**Puleio R, Schiavo MR, Macaluso G, Manno C, Loria GR,** ***Veterinary Record*** **(2013) 172: 398**
"Environmental contamination by asbestos, obtained by mineral extraction for its use in buildings and industrial activity, still represents one of the health priorities of modern times. Asbestos-related risks and its implications in human disease, such as mesothelioma and similar conditions, are still controversial. In 2004, epidemiological studies revealed an unexpected high prevalence of pleural mesothelioma in human beings of Biancavilla village in Catania, a small town at the foot of Mount Etna. This discovery provoked the public health authorities to investigate the environmental risk in the area. The source of the problem was identified as a local open-pit mine located near Monte Calvario, which had been used over the last century as a source of concretepozzolan sand for buildings in the town. …. Its aim was to evaluate and identify possible risks of aerogenic contamination by 5-fluoroedenite fibre in animal sentinels. The authors monitored the presence of the mineral in wild rodents trapped in the Biancavilla area as potential indicators of dust contamination …..The study showed that wild rodents can act as suitable and effective indicators of environmental contamination. …. Wild rodents may be also used as reliable sentinels to monitor potential environmental risks, such as dust pollution of large cities. …. In future, it may be desirable to test other species, including poultry, pigeons and rabbits, as these may be more sensitive indicators of environmental pollution."

**Summary:**
**There are few projects funded that utilize wild animal models. Using QVR and searching over FY07-FY15 a total of 43 applications were submitted and 8 were funded. This is in sharp contrast to the total number of animal models studied over the same time period (60,060). While there may be some applications that failed to meet the search criteria, these analyses indicated that there is a paucity of research funded by the NIH that utilized wild animal models.**

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